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Serum AMH and 25 (OH) vitamin D levels in polycystic ovarian syndrome

Serum AMH and vitamin D in PCOS

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Abstract

Aim: In this study, we aimed to investigate the possible relationship between serum 25(OH) vitamin D and AMH levels in patients diagnosed with polycystic ovarian syndrome.

Material and Methods: A total of 42 patients, including 21 patients diagnosed with PCOS and 21 control group patients who did not have clinical and laboratory findings of PCOS, were included. Women were diagnosed with PCOS based on the revised Rotterdam criteria. Patients in the control group were selected from patients with tubal, male factor, endometriosis, or unexplained infertility. All participants underwent venous blood sampling for the determination of AMH and 25-OH vitamin D levels. The primary outcome of the study was investigation of the relationship between 25(OH) vitamin D concentration and serum AMH levels.

Results: Serum LH, total testosterone, HOMA-IR, and fasting insulin levels in PCOS patients were significantly higher than in the control group. The mean age of the participants in both groups was similar (25.8±2.03 vs. 26.5±2.88, p<0.054). BMI values of PCOS patients were significantly higher than of those in the control group (28.02±5.11 kg/m2 vs 26.01±3.09 kg/m2, p<0.04). Serum AMH levels of PCOS patients (6.13±2.11 ng/mL) were significantly higher than in the control group (3.44±0.43 ng/mL, p<0.01). On the other hand, serum 25(OH)D levels of the patients in the PCOS (16.5±4.02 ng/mL) group were found to be significantly lower than in the control group (21.03±2.30 ng/mL, p<0.03). While serum AMH was positively correlated with total testosterone, it was negatively correlated with age in PCOS. Serum AMH levels were negatively correlated with BMI in PCOS. No significant correlation was observed between 25-OH Vitamin D and AMH levels in the PCOS group.

Discussion: While serum AMH levels of PCOS patients increased, 25 (OH) vitamin D levels decreased. AMH and vitamin D levels did not correlate.

Keywords

PCOS, AMH, 25 (OH) Vitamin D, BMI, HOMA-IR

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Introduction

Vitamin D, a steroid hormone, is produced from skin exposed to sunlight and then activated in the liver and kidneys. In addition to its conventional effects on calcium metabolism, the presence of vitamin D receptors in the ovaries, endometrium, placenta, hypothalamus, and pituitary suggests that this hormone also plays an important role in the female reproductive system [1]. In line with this, vitamin D deficiency in animals reduces fertility rates and causes developmental delay in newborn babies [2]. Impairment of follicle development in vitamin D receptor knockout mice [3] and the development of hypergonadotropic hypogonadism have suggested a link between vitamin D and oocyte developmental capacity. The increase in sex steroid synthesis after the addition of vitamin D to ovarian cell cultures in humans suggested that this vitamin may have a role in folliculogenesis [4].

Polycystic ovarian syndrome (PCOS) is a common endocrine and metabolic disorder with subfertility, and serum vitamin D levels are low in most cases [5]. An association between serum vitamin D level and anovulation, hyperandrogenism, and insulin resistance has been reported in most patients with PCOS [6]. Anti-mullerian hormone (AMH) is a growth factor produced by granulosa cells and regulates follicle development. It peaks in the early preantral and small antral follicles stage and decreases the FSH sensitivity of the follicles. Since there is little change in levels throughout the cycle and reflects the primordial follicle pool, serum AMH values have begun to be used as ovarian reserve markers in the last decade [7]. The relationship of vitamin D with follicle development and the presence of a vitamin D-response element in the promoter region of the AMH gene indicate that these two molecules are related [8]. For this purpose, many studies have been conducted comparing serum vitamin D levels and AAMH values in PCOS patients. However, the study results showed discordant results unlike experimental models and cell culture studies. Some studies reported a positive relationship between AMH and vitamin D, while others suggested a reverse relationship or no relationship at all [9]. This study was planned to investigate the possible relationship between serum vitamin D and AMH levels in patients diagnosed with PCOS.

Material and Methods

A total of 42 patients, including 21 patients diagnosed with PCOS and 21 control group patients who did not have clinical and laboratory findings of PCOS. Women were diagnosed with PCOS based on the revised Rotterdam criteria, which require two of the following three manifestations: (1) oligo and/or anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) polycystic ovaries determined by ultrasonography. Patients in the control group had to meet none of the Rotterdam criteria to be included in the study. Patients in the control group were selected from patients with tubal, male factor, endometriosis, or unexplained infertility. Women who had undergone surgical procedures that would affect ovarian reserve, those with a history of chemoradiotherapy, those with endocrine disease including diabetes, and those who received vitamin D supplementation were not included in the study. The study was performed according to the guidelines of the Helsinki Declaration on human experimentation. Patient consent and local ethics committee approval were obtained.

Demographic parameters such as age and body mass index of the patients were recorded. Venous blood samples were obtained after an overnight fasting between the 3rd and 5th days of the natural menstrual cycle for control patients or progestin withdrawal bleeding for PCOS patients. Serum follicular stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and insulin were measured with chemiluminescent enzyme immunoassay. Total testosterone, and dehydroepiandrosterone sulfate (DHEA-S) were measured via the radioimmunoassay method. Insulin resistance was evaluated by calculating a homeostatic model assessment of insulin resistance (HOMA-IR = fasting blood glucose (mg/dL) x fasting insulin (mIU/L)/405). Total plasma 25-OH vitamin D was measured with chemiluminescent enzyme immunoassay and results were given in ng/mL. Serum AMH levels were measured with Gen II Beckman Coulter AMH ELISA kit according to the manufacturer's instructions. The primary outcome of the study was to investigate the relationship between 25(OH) vitamin D concentration and serum AMH levels.

Statistical analysis

Analyses of data were performed on SPSS 21 (SPSS Inc., Chicago, IL, USA). To check for normality, the Shapiro-Wilk test was used. Normally distributed variables were analyzed with the independent samples t-test. Non-normally distributed variables were analyzed with the Mann-Whitney U test. Spearman's correlation coefficients were calculated to evaluate relationships between continuous variables. Data are presented as mean±SD. Differences were considered statistically significant if the p-value <0.05.

Results

Demographic, laboratory characteristics of PCOS and control groups are shown in Table 1. Serum LH, total testosterone, HOMA-IR, and fasting insulin levels of PCOS patients were significantly higher than in the control group. The mean age of the participants in both groups was similar (25.8±2.03 vs. 26.5±2.88, p<0.054). BMI values of PCOS patients were significantly higher than those in the control group (28.02±5.11 kg/m2 vs 26.01±3.09 kg/m2, p<0.04). Serum AMH levels of PCOS patients (6.13±2.11 ng/mL) were significantly higher than in the control group (3.44±0.43 ng/mL, p<0.01). On the other hand, serum 25(OH)D levels of the patients in the PCOS (16.5±4.02 ng/mL) group were found to be significantly lower than in the control group (21.03±2.30 ng/mL, p<0.03).

While serum AMH was positively correlated with total testosterone, it was negatively correlated with age in PCOS. Any correlation was not detected between AHM, HOMA-IR and insulin levels. No significant correlation was observed between 25-OH Vitamin D and AMH levels in the PCOS group. Serum AMH levels were negatively correlated with BMI in the PCOS. As BMI values increased, AMH values decreased significantly. Any correlation was not detected between BMI and 25 (OH) vitamin D levels in PCOS. Negative and significant correlation between AMH and age was noted in the control group.

Table 1. Demographic and biochemical characteristics of PCOS and control groups

	PCOS (n=21)	Control (n=21)	p value
Age	25.8±2.03	26.5±2.88	0.54
BMI	28.02±5.11	26.01±3.09	0.04
AMH	6.13±2.11	3.44±0.43	0.01
Vitamin D	16.5±4.02	21.03±2.30	0.03
FSH	4.98 ± 1.22	4.55 ± 0.44	0.35
LH	8.66 ±1.30	5.97 ±0.65	0.04
Estradiol	33.4±6.12	30.6±2.05	0.75
Insulin	14.6±4.55	5.90±1.60	0.01
HOMA-IR	3.11±1.03	1.66±0.60	0.04
Total Testosterone	0.55 ± 0.01	0.29 ± 0.10	0.01
DHEA-S	354.6±34.5	312.6±60.4	0.86

Table 2. Correlation between AMH, 25 (OH) D and other parameters

	AMH	25(OH) vitamin D
Age	R = -0.56, p<0.03*	R= -0.45, p<0.72
BMI	R= -0.67, p<0.02*	R= 0.30, p<0.33
Testosterone	R= 0.69, p<0.01*	R= 0.29, p<0.50
HOMA-IR	R= 0.32, p<0.32	R= 0.40, p<0.60
Insulin	R=0.43, p<0.64	R=0.20, p<0.20

No significant correlation was found between serum AMH, vitamin D, BMI, other demographic, hormonal, and dyslipidemia parameters in the control group. Correlation characteristics of PCOS group are shown in Table 2.

Discussion

The main findings of our study can be listed as follows. Serum AMH levels of PCOS patients were significantly higher than in the control group. This finding is consistent with literature data. Almost all of the studies investigating AMH values in PCOS patients reported that this glycoprotein molecule increased significantly. The fact that AMH was found to be high in PCOS, and this increase was independent of the cycle brought up the suggestion that this molecule should be included in the PCOS diagnostic criteria. However, high AMH does not always indicate the true value of the primordial follicle pool. Elevated AMH is evidence that follicles are arrested at a certain stage rather than ovarian reserve [7]. AMH better represents the response to ovarian stimulation rather than the primordial follicle pool.

As ovarian aging increases with advancing female age, AMH values decrease. We found decreased AMH values in PCOS patients, which correlated with increasing age. The decrease in AMH was not specific to the PCOS group, and AMH values also decreased with age in the patients in the control group. We could not detect a correlation between AMH and 25 (OH) vitamin D levels. In accordance with our findings, serum vitamin D levels in PCOS patients have been reported to be decreased in many studies [4,9]. Vitamin D reduction may cause some clinical manifestations of PCOS. PCOS findings such as anovulation, hyperandrogenism, and insulin resistance are more common in vitamin D deficiency [6]. AMH values may be normalized as these findings are improved in patients who are given vitamin D therapy. A recent meta-analysis reported a decrease in AMH values after vitamin D administration to anovulatory PCOS patients [9]. However, vit D did not have the same effect in ovulatory patients. For this reason, in order to talk about a relationship between AMH and vitamin D in PCOS patients, it is necessary to divide the patients into groups as ovulatory or anovulatory. In addition to studies showing a positive correlation between Vitamin D and AMH values, there are also studies showing a negative correlation [9]. We could not find a significant relationship between AMH and vitamin D levels. While our findings are compatible with some studies, they are inconsistent with others. Since we did not divide our patients into sub-groups according to their ovulatory status, it is not possible to make a clear comment on this issue. On the other hand, grouping patients according to their vitamin D levels and comparing them with AMH could provide more precise data. No correlation was found between AMH and vitamin D in studies that classified patients in the PCOS and control groups with vitamin D levels as deficient or normal [10]. We found a negative and significant correlation between AMH and BMI. There are studies in the literature reporting negative or positive correlations between BMI and AMH. Decreased AMH with increasing BMI may occur due to hemodilution in obese PCOS patients [11-13]. However, we did not divide the patients into groups according to their BMI values. A negative correlation may occur between AMH and BMI, depending on the changes in adipose tissue adiponectin and leptin levels in thin PCOS patients. In order to make a clear comment on this issue, it is necessary to divide patients into groups according to their BMI values and examine their relationship with AMH [14,15]

Conclusions

Our study has some limitations. The small number of patients in the PCOS and control group is an important limitation. Another limitation is that we did not divide patients into subgroups according to their BMI and vitamin D levels. It is also a handicap that vitamin D measurements are not made together with the binding protein. Despite all these limitations, our results are important in terms of comparing the relationship between AMH and 25(OH) vitamin D levels in PCOS patients with demographic and hormonal parameters. It will be possible to reach clearer results with studies that group PCOS patients according to BMI and 25(OH) vitamin D levels and compare AMH values.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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